CBER's Bioresearch Monitoring Program

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CBER/OCBQ/DIS/BIMO

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CBER's Bioresearch Monitoring

- Office of Compliance and Biologics Quality
- Division of Inspections and Surveillance
- Bioresearch Monitoring (BIMO) Team

CBER's Bioresearch Monitoring

Purpose:

- To ensure the quality and integrity of data submitted to FDA in support of an IND, IDE, BLA, or other application
- To ensure that the rights and welfare of human research subjects are protected

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Function:

- Detect errors or misconduct in a clinical study that might impact on human subject protection, data integrity, or decision-making
- Prevent data quality/integrity problems

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When do we become involved and what do we do?

- Submission of Biologics License Application (BLA): we conduct pre-approval data audit inspections

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When do we become involved and what do we do?

- Investigate complaints from sponsors, Institutional Review Boards (IRBs), and consumers

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When do we become involved and what do we do?

- Routine surveillance of ongoing studies for blood, vaccine, cell therapy, and gene transfer products

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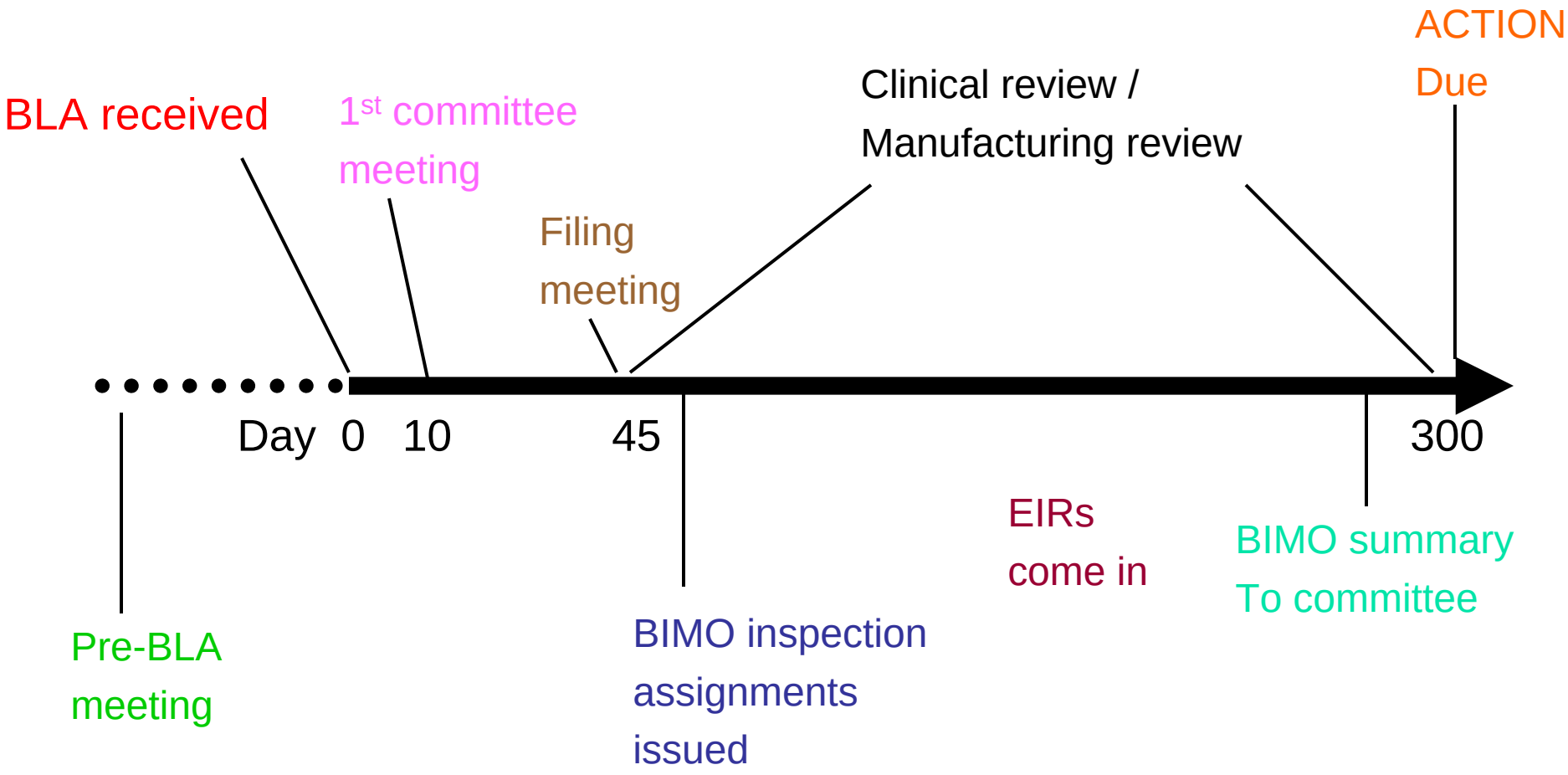
When do we become involved and what do we do?

- Referrals and questions from CBER staff
- Referrals from other Centers

The BIMO Program Covers:

- Clinical Investigators
- Sponsors
- Monitors
- CROs (Contract Research Organization)
- IRBs (Institutional Review Boards)
- Non-clinical Laboratories (GLP = Good Laboratory Practices)

BLA BIMO Involvement



Selection of Clinical Sites for BIMO Inspections:

- Goal
  - To inspect sites representing 50% of the subject population
- Considerations
  - Multiple sites, each with small enrollment
  - Large trial with a large subject population

Factors in Site Selection

- Number of subjects at the site
- Number of studies the clinical investigator is conducting
- GCP problems reported by the sponsor
- Randomization cannot be reconstructed
- Number of sub-investigators / sub-sites
- Pending workloads in FDA Districts

Factors in Site Selection

- Geographic distribution of subjects
- Distribution of subjects whose data are excluded from Safety and Efficacy analyses
- Inspection history of investigators
- Inconsistent data from a site

How Many Inspection Sites?

Study populations vary -

- 7 to 15,000 subjects for pivotal study

Attempt to cover 50% of study population although this goal is often not possible

- Low enrollment at many sites
- Large studies with dozens of sites
- Usually 3-5 sites selected – including foreign sites

How do we Focus the Inspection?

Inspection Assignment:

- Background of product and protocol
- Specific concerns and questions from review staff:
  - Safety data: Serious Adverse Events (SAEs) and Adverse Events (AEs)
  - Protocol deviations cited in BLA
  - Randomization or Blinding concerns

How do we Focus the Inspection?

- Specific concerns and questions from review staff continued:
  - Efficacy data: Clinical endpoints
  - Required laboratory tests
  - Data line listings

Verified During Inspection

- Laboratory test results
- Physician’s notes
- Diagnostic imaging studies
- Monitoring of records
- Test article storage and accountability

Verified During Inspection

- Demographics
- Eligibility criteria
- Randomization
- Protocol adherence
- Selected data from application

Verified During Inspection

- IRB approval
- Informed Consent Documents
- Case Report Forms
- Other source documents
- Primary/Secondary Endpoints

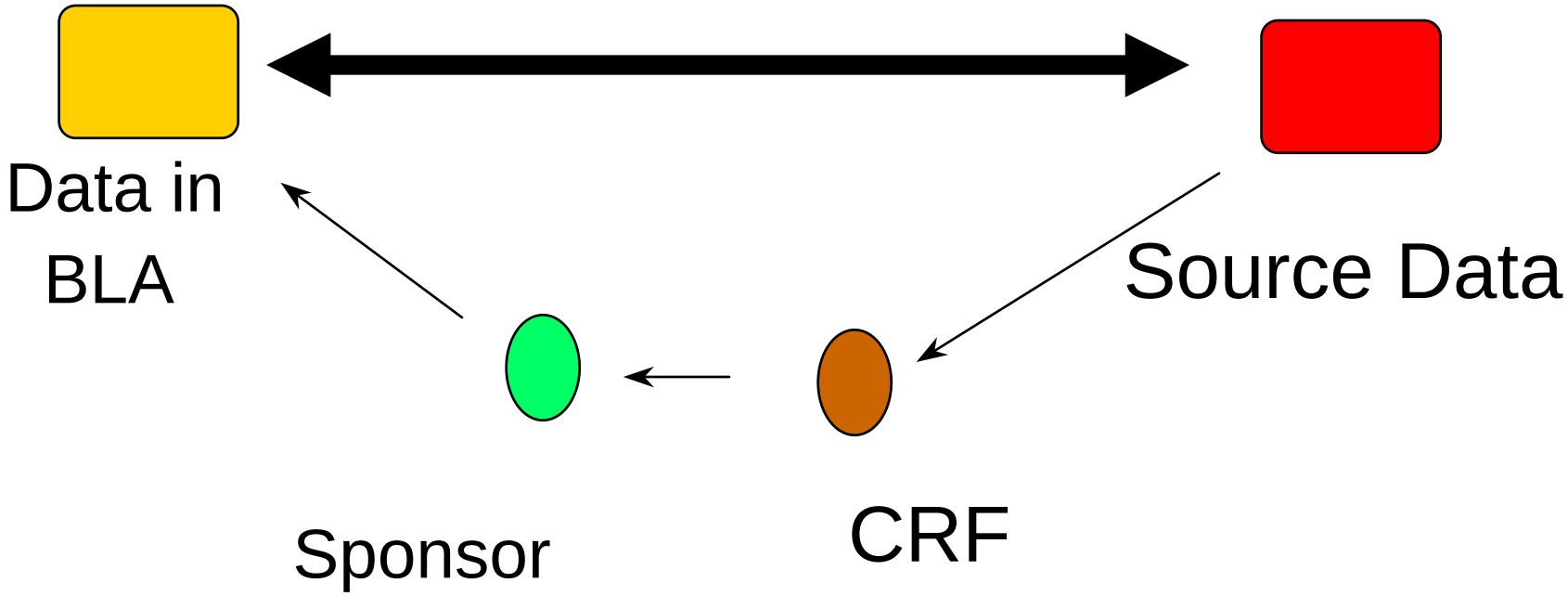
Source Data & Source Documents

- Source data are contained in source documents
- A source document is the original record where data are recorded
- The electronic record contains source data when original observations are directly entered in to computer system

Examples of Source Documents

- Physician and hospital records
- Laboratory records
- X-rays, CT scans
- EKGs
- Correspondence referrals
- Test article accountability records
- Informed consent forms

Comparison of Data in BLA to Source



Elements of Data Quality

- Attributable
- Legible/readable
- Contemporaneous
- Original
- Accurate

Why Sites Fail

- Failure to follow the protocol
- Inadequate record keeping practices
- Inadequate informed consent process
- Inadequate oversight of study personnel

Why Sites Fail

- Failure to obtain IRB approval
- Randomization errors
- Study blind is broken
- Failure to inform sponsor/IRB of adverse advents

Significance of Deviations

Do the violations

- Directly impact the integrity of the data set?
- Indicate systemic problems within the study?
- Indicate that other studies at that site might be impacted?

Significance of Deviations – Violations of 21 CFR:

- Part 312 – Investigational New Drugs
- Part 812 – Investigational Device Exemptions
- Part 50 – Informed Consent
- Part 56 – Institutional Review Boards
- Part 58 – Non-clinical Laboratories (GLP)

The Form FDA 483

- List of Inspectional Observations
- Presented by the FDA investigator to the responsible individual at the inspected site at the conclusion of the inspection

After the Inspection

- FDA investigator prepares an Establishment Inspection Report (EIR)
- BIMO Staff
  - Review and classify the EIR
  - Issue correspondence

BIMO Staff & BLA Committee

- After the EIRs are received for the inspection sites:
  - BIMO makes recommendations to the BLA Committee about the accuracy and reliability of the data collected from the sites
  - BIMO summarizes inspectional findings in a report to the BLA committee

Inspection Follow-Up Letter

- Untitled Letter:
  - NAI (No Action Indicated)
  - VAI (Voluntary Action Indicated)

Inspection Follow-Up Letter

- Titled Letter

  OAI (Official Action Indicated)

  - Warning Letter
  - Notice of Initiation of Disqualification Proceeding and Opportunity to Explain (NIDPOE)

Posting of Redacted OAI Letters

Freedom of Information Act (FOIA)

- FDA's Electronic Freedom of Information Reading Room
- www.fda.gov
- Warning Letters
  - www.fda.gov/foi/warning.htm
- NIDPOE Letters
  - www.fda.gov/foi/nidpoe/default.html

Possible Administrative Actions

- Determine if data are reliable
- Delay approval of BLA
- Clinical Hold
- Disapproval of IDE
- Initiate termination of IND
- Initiate disqualification of investigator
- Initiate Application Integrity Policy
- Refer to Office of Criminal Investigations

CBER's BIMO Program

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- Branch Chief
  - Pat Holobaugh 301-827-6347